Author’s response to reviews

Title: Folate intake and depressive symptoms in Japanese workers considering SES and job stress factors: J-HOPE study

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Author’s response to reviews:

Dear Editor:

We greatly appreciate all the reviewers and the editor for their critical and constructive comments to our work, which will help to improve the manuscript. The current study provides a strong evidence for the relation between energy-adjusted folate intake and depressive symptom in Japanese workers together with the consideration of SES and job stress factors. By virtue of your advice and comments, our manuscript has been improved. Please find the attachment in this mail for the revised manuscript. We hope you will find the revised manuscript acceptable for publication in BMC Psychiatry Journal. Thank you very much.

For Reviewer 1:

Major Compulsory Revisions

1. The whole manuscript should be edited thoroughly by a native English speaker.

We have improved our English expression checked by an English-speaker.

2. Moreover the introduction and discussion do not seem to include the most important literature.

We added the two literatures about the intervention studies of folate administration recommended by the Reviewer 1 in instruction section, and cited some new references in discussion section to argument the mechanisms of
folate intake relate to depressive symptom, especially the new hypothesis for the epigenetic role of homocysteine.

3. It is unclear whether the food questionnaire used had been validated in relation to folate intake. If so, validation data should be presented.

The questionnaire used in the current study has been validated in relation to folate intake and the data can be seen in ref. 25, a report for evaluation methods of nutrition and dietary lifestyle programs in Japanese published by Ministry of Health, Welfare, and Labour of Japan. We added the Pearson correlation coefficients for folate in the method.

4. Some data of analyses is given in de discussion only, e.g., related to associations in women and men separately. These should have been given first in the results section.

The results of associations considering the gender difference were moved to the results section, and in discussion section we debated the reasons of this difference. We also indicated the relative small size of female subjects limited the power of our analysis.

Minor Essential Revisions:

5. It is unclear whether and how the drop-outs differed from the participants.

The current study is a cross-sectional analysis, we don’t have any drop-outs which is a concept used in the prospective study.

6. Please indicate whether the self-administered or interviewer-administered version of de K6 was used.

In the text, the sentences “It comes in a self-administered version and an interviewer-administered version” is the description of the K6 scale cited from Ref. 21. Then I added an explanation that we used the self-administered version.

7. Has the Japanese version of the K6 been validated, and which method was used to translate the version in Japanese. The reference given for validation does not have a very strong design in the study by Baggaley et al.

At first, we would like to apologize for our mistake of citing a different reference Baggaley et al. by mistake. We have replaced it into a study in Japanese population. The Japanese version of the K6 had been validated in Ref. 22, in which the depression was diagnosed by SCID as gold standard, and sensitivity and specificity were estimated as 77.8 and 86.4 in Japanese population.

8. SPSS has not been developed by IBM Corporation, New York, USA.

IBM purchased SPSS Inc in 2009. SPSS was integrated into IBM's Information Management software portfolio.

9. It is unclear whether there was also a question about the use of vitamine B preparation of folate supplements, and whether such participants were excluded.
There was no separate question about the use of vitamin B as nutrient supplementation in current study, but we have excluded the patients with vitamin B medication here.

10. It is stated that the results were in agreement with previous study of Japanese Yet study 4 was done in eastern Finland. Moreover it was stated that the small sample size of this study was 517 (Ref. 4), which seems to be incorrect.

We are sorry for making a mistake on the reference number. The correct reference we wanted to cite here was No. 5 and we have corrected it.

11. Table 1. Please also indicate whether there was a difference between the groups for total energy intake and unadjusted folate intake.

According to Reviewer's suggestion, we added the results of unadjusted folate intake into Table 1 and results section. However, these unadjusted results have no influence on our final results.

12. Table 2. It seems unnecessary to give the beta coefficients for all covariates, as the focus of the manuscript was on folate intake in relation to depressive symptoms. Please also give the crude (i.e., unadjusted), and age and sex adjusted beta values.

Table 2 has been replaced. In the new Table 2, we removed the unnecessary data and just provided beta coefficients and P values for adjusted folate intake only.

13. Table 3 does not seem to add much to the findings and analyses, besides reiterating the results from table 2, albeit with a much lower power, as a dichotomization of the dependent variable (depressive symptoms) was used.

We evaluated the association of folate intake with depression as a continuous variable in Table 2.

In Table 3, we additionally evaluated the association of folate intake with depression as a dichotomous variable with cut-off point of 9, which is often used in K6 analysis and of clinical importance. We do not erase the table.

To Reviewer 2:

The result that there was an inverse association between depression score and folate intake is significant to some extent, but the interpretation of the results should be done with caution. One of the reasons is, as the authors have mentioned, the cross-sectional nature of the study. Another is that candidate risk factors of depression, folate intake, SES and job stress could be influenced each other. The authors made multiple regression analyses in order to see each effect on depression score by adjusting other factors. However, these analyses may mislead the result, unless single regressions and correlation analyses were conducted before doing multiple regressions. I recommend that the authors...
should do those steps or use another more sophisticated method for this type of analysis.

We have revised the interpretation of our results. The single regression for each factor was conducted in order to see their respective influence on K6 score. The results were stated in results section and the significant factors were indicated. As the Reviewer 2 suggested, the crude data for association of folate intake with depression was presented in Table 2.

By virtue of the Reviewers’ and the Editor’s advice, we have revised and improved our manuscript, albeit the same conclusion of the current study indicated that low folate intake was suggested to be associated with higher depression score and the prevalence of depressive symptoms in Japanese occupational cohorts together with the consideration of SES and job stress factors.

Sincerely

Yixuan Song